EXHIBIT B

Circulation: Cardiovascular Quality and Outcomes

RESEARCH LETTER

Abrupt Increase in Reporting of Neoplasms Associated with Valsartan After Medication Recall

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In July 2018, trace amounts of the potential carcinogen N-nitrosodiethylamine were found in some formulations of angiotensin receptor blockers (ARBs), particularly valsartan. This led to recall of valsartan in the United States,[1] which received wide media and public attention. We investigated the trends in ARB-associated neoplasm adverse events (AEs) reported to the Food and Drug Administration.

Using the Food and Drug Administration Adverse Events Reporting System (FAERS), we identified trends in AE reporting associated with valsartan and other ARBs between January 1, 2017 and December 31, 2018. We compared the percentage of neoplasms out of all AEs by drug type (valsartan versus other ARBs: losartan, candesartan, irbesartan, olmesartan, telmisartan) using χ^2 test. We further assessed and compared reporting of valsartan AE by consumers and healthcare professionals and calculated reporting odds ratio (ROR), as previously described.[2] Logistic regression models were used to assess ROR. The χ^2 tests were used to compare categorical variables. Institutional Review Board approval was not required as this study uses a deidentified public dataset.

Since 2017, there have been a total of 11112 AEs reported (5151 valsartan, 5961 other ARBs), of which 920 (8.7%) were because of neoplasms (14.7% out of valsartan AEs, 3.6% out of other ARBs AEs). Number of AEs increased more significantly in valsartan (1117 in 2018 Q1–Q2 to 2671 in 2018 Q3–Q4) compared with other ARBs (1634 in 2018 Q1–Q2 to 2322 in 2018 Q3–Q4), $P<0.001$ (by χ^2 test). Percentage of all reported AEs (valsartan to other ARBs) increased from 5.3% pre-recall to 23.4% post-recall (Figure [A]).

Reporting odds ratio for neoplasm AEs increased from 1.7 (1.3–2.2) pre-recall to 7.1 (5.7–8.9) post-recall. Monthly analysis showed an abrupt increase in ROR in July 2018 (ROR, 15.4 [7.7–30.9]) compared with June 2018 (ROR, 1.8 [0.9–3.9]), which continued through August (ROR, 18.2 [9.2–36.0]) and September (ROR, 17.2 [6.9–42.8]) and decreased (but remained elevated above baseline) in October (ROR, 6.2 [3.7–10.5]) through December 2018 (ROR, 2.9 [1.9–4.7]).

Among reports submitted only by consumers, ROR increased to 16.5 (8.0–33.7) in Q3 2018 and decreased to 2.4 (1.7–3.4) in Q4 2018 but remained elevated compared with 1.0 (0.4–2.7) in 2018-Q2 (Figure [B]).

We describe an abrupt and biologically implausible rise in valsartan-associated neoplasms in the third quarter of 2018, after a drug recall that attracted extensive national media coverage.

AE reporting has problems related to inherent shortcomings of the Food and Drug Administration Adverse Events Reporting System data: inaccurate, voluntary, and delayed reporting are some examples. Our findings not only underscore these limitations but also illustrate how an increase in drug AE reporting can be associated with drug recalls and the media.

More broadly, these observations highlight the limitations of the Food and Drug Administration's Adverse Events Reporting System and suggest that relying on passive pharmacovigilance analytics to identify risk may result in false signals, especially when relying on reporting by consumers.

Key Words: attention ■ carcinogens ■ neoplasms ■ United States ■ valsartan

https://www.ahajournals.org/journal/circoutcomes

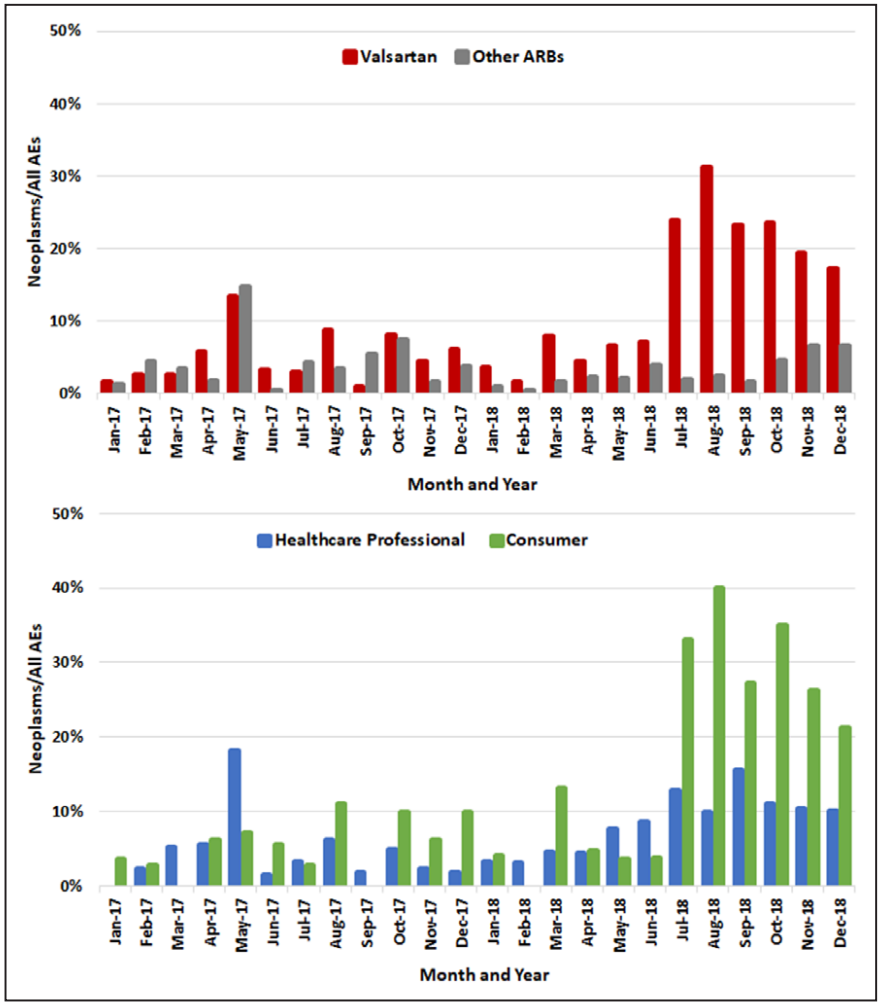

Figure. Relative reporting of neoplasms to all-cause adverse events (A) stratified by type of ARB (valsartan vs other) **(B)** stratified by reporting entity (healthcare professional vs consumer) in the valsartan subgroup.

Although consumer reporting appeared to be the most susceptible to the widely covered recall, healthcare providers were also influenced. Interestingly, the duration of this effect was transient, as most cancer AEs were reported early after the recall and decreased over time, remaining above baseline. In a similar analysis of the FDA Manufacturer and User Facility Device Experience database, cardiovascular device recalls were also associated with increased reporting of AEs but differently, those preceded the recall, and persisted for a few months.[3]

In conclusion, after the widely covered valsartan recall in 2018, we found a steep and transient rise in reporting of ARB-associated cancers, which we think to be biologically implausible. This observed phenomenon was likely associated with public alarm and fueled mainly by consumer and lay reporting. Government-sponsored strategies for patient and provider education are urgently needed to avoid premature discontinuation, legal disputes, and inaccurate drug-AE associations associated with valsartan and more broadly, with other recalled medical therapies.

ARTICLE INFORMATION

The data that support the findings of this study are available from the corresponding author on reasonable request.

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Disclosures

None.

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